REMARKS

The abstract was objected to because it was not in the form of a single brief paragraph. The original abstract has been amended and now summarizes the subject matter of the new claims 5 to 13 filed above. It is in one paragraph and complies with U.S. Patent Office Rules.

Withdrawal of the objection to the abstract is respectfully requested.

In addition, standard section headings have been added to the specification as recommended by U.S. Patent Office Rules.

Claims 1 to 4 have been rejected under 35 U.S.C. 101 because these claims recite a use without reciting positively any method steps for performing the method of use.

Claims 1 to 4 for the "use" or "uses" have been canceled without replacement, obviating their rejection under 35 U.S.C. 101.

New claims 5 to 13 include pharmaceutical composition claims 5 to 8 for treating hyperinsulinemia and method-of-treating-hyperinsulinemia claims 9 to 13.

The main method claim 9 includes the step of administration of an effective amount of the at least one compound for inhibiting insulin release to the living being suffering from the hyperinsulinemia.

Claims 12 and 13 claim preferred methods for performing the step of

administration to the living being, e.g. intravenously, sublingually, etc. Basis for these specific administration methods is found on page 3, lines 9 to 12, of applicants' specification.

It is respectfully submitted that none of the new claims 5 to 13 should be rejected under 35 U.S.C. 101.

Claims 1 to 4 were rejected as indefinite under 35 U.S.C. 112, second paragraph.

Claims 1 to 4 have been canceled. The wording of the new claims 5 to 13 has been selected to avoid further indefiniteness rejections.

Claims 5 to 13 do not include the term "derivative". The scope of these claims is clear. The "at least one compound" of independent claims 5 and 9 is a compound that inhibits insulin release by interacting with a melatonin-specific receptor in the β-cells of the pancreatic islets of the living being suffering from hyperinsulinemia.

The specification of the above-identified application actually discloses two such compounds. The first compound is of course melatonin and the second such compound is pertussis toxin disclosed in the third full paragraph in the specification. A number of compounds are known to influence melatonin-specific receptors by inhibiting stimulated insulin release in model systems.

From the standpoint of indefiniteness the scope of the term "compounds that influence melatonin-specific receptors to inhibit insulin release" is well defined. Either a compound does or it does'nt act in this manner to inhibit the

insulin release.

The term "and/or" is not used in the new claims.

The result of the "influencing" is now well-defined, it is the inhibition of insulin release.

Hyperinsulinemia, otherwise referred to as hyperinsulinism (see Webster's Dictionary), is a disease in which the body generates too much insulin. It causes hyperglycemia, an excess of sugar produced in the body. This is a well-defined medical condition. In fact the Office Action on page 4 includes a definite definition of this term.

The term "inhibiting insulin release" is well-defined and means reducing the amount of insulin or the rate at which insulin is released by the pancreatic islets.

The term "therapy system" or "system" is not used in the claims.

For the foregoing reasons it is respectfully submitted that none of the new claims 5 to 13 should be rejected under 35 U.S.C. 112, second paragraph.

Claims 1 to 4 were rejected under 35 U.S.C. 112, first paragraph, were rejected because the specification did not enable claims for a method of suppressing insulin release by administering chemically modified derivatives of melatonin.

The term "chemically modified melatonin derivative" is not used in the new claims.

The term "at least one compound" is used instead of the term "chemically

modified melatonin derivative".

The specification describes several compounds that inhibit or block melatonin receptors, namely melatonin itself, pertussis toxin (page 2 in the background section) and pertussis-sensitive G-protein. However only melatonin is described as inhibiting insulin release. Nevertheless this disclosure should be enough to support claims for "at least one compound" that suppresses insulin release. It provides some guidance for selection of compounds that are related structurally to melatonin that might inhibit insulin release.

For the foregoing reasons and because of the changes in the claim wording, it is respectfully submitted that none of the new claims 5 to 13 should be rejected under 35 U.S.C. 112, first paragraph.

Claims 1 to 2 were rejected under 35 U.S.C. 102 (b) as anticipated by Bailey, et al.

Claims 1 and 2 have been canceled without replacement.

Bailey does disclose inhibition of glucose-induced and basal insulin release from rat pancreas cells using melatonin in *in vitro* experiments. However Bailey does not disclose treatment of hyperinsulinemia, in other words, effective *in vivo* administration to a living being to treat this medical condition. Bailey,et al, does not disclose any preferred administration methods for administering melatonin to a living being to treat this medical condition.

Thus new method claims 9 to 13 should not be rejected as anticipated by Bailey, et al, especially since claim 3 was not rejected as anticipated by Bailey, et

al.

Furthermore Bailey, et al, does not disclose any pharmaceutical compositions containing melatonin to be administered to a living being or effective amounts of melatonin for pharmaceutical compositions for treating hyperinsulinemia.

For the foregoing reasons it is respectfully submitted that none of the new claims 5 to 13 should be rejected as anticipated under 35 U.S.C. 102 (b) by Bailey, et al.

Claim 3 was rejected under 35 U.S.C. 103 (a) as obvious from Bailey, et al.

Claim 3 has been canceled, but claims 9 to 13 are method-of-treating-hyperinsulinemia claims. These latter new claims replace claim 3.

On the contrary, Bailey, et al, contains teaching that would lead one skilled in the art away from the claimed invention. One skilled in the art would be discouraged from using melatonin to inhibit insulin release by administering to a living being or from preparing pharmaceutical compositions for that purpose.

The last paragraph on page 24 of Bailey, et al, discloses "In vivo" studies of administration to melatonin to rats. It was found that plasma insulin levels were *not significantly changed*, although there was a slight apparent lowering of two out of five measured values shown in Fig. 3. Also glucose levels for the five measured values were not lowered at all.

Also note the discussion regarding *in vivo* administration of melatonin on

page 26, next to last paragraph, of the Bailey reference.

Thus Bailey, et al, contains teaching that would lead one skilled in the art to find that an effective treatment of hyperinsulinemia by administering melatonin or a pharmaceutical composition containing melatonin was surprising and unexpected.

There is a great difference between *in vivo* administration of a compound to treat a medical condition and *in vitro* experiments with isolated cell cultures that suggest that the compound *might* be effect for treating the condition. For example, a compound that is orally administered may be completely metabolized and converted to a different compound prior to reaching the organ containing the cells.

More recent *in vivo* experiments by the applicants and others however support the belief that melatonin can be administered to a living being to reduce insulin levels, although contradictory results appear in the literature. These more recent results are discussed in a recently published article by Peschke, et al, that is being filed together with an Information Disclosure Statement. This reference and Information Disclosure Statement accompany this amendment.

For the foregoing reasons it is respectfully submitted that none of the new claims 5 to 13 should be rejected as obvious under 35 U.S.C. 103 (a) by Bailey, et al.

APPENDIX SHOWING THE CHANGES IN THE ABSTRACT

Underlining shows additions, brackets show deletions

Page 8, the following changes were made in the abstract:

[SUMMARY] ABSTRACT OF THE DISCLOSURE

The [present invention relates to the use of] pharmaceutical compositions for treating hyperinsulinemia contain an effective amount of melatonin and/or a chemically modified derivative thereof for inhibition [making pharmaceutical preparations for regulation] of insulin release. The melatonin and/or chemically modified derivative of melatonin act to inhibit insulin release by influencing the β-cells [β-cell] of the pancreatic islets in a living being suffering from hyperinsulinemia through a melatonin-specific receptor. The effective amount of melatonin and/or chemically modified derivative thereof in the pharmaceutical composition amounts to from 0.01 to 200 mg. The pharmaceutical compositions can be in the form of a tablet or capsule. Alternatively, they can be in a form for subcutaneous injection, such as an ampule, or for transdermal release.

[Surprisingly, we have found that melatonin and/or chemically modified derivatives thereof, when used according to the invention,

- realize their insulin-reducing influence through G-protein-coupled membrane-bound receptors;
- through the melatonin receptor assume pacemaker significance,

because the release of insulin from isolated pancreatic islets underlies the circadian and ultradian rhythms;

through the melatonin receptor, in pharmacological (5 μm) as well as in physiological doses (0.2 nm), reduce the stimulated release of insulin from pancreatic islets in statistically significant manner.]

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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